REMARKS

The Official Action dated May 1, 2006 has been carefully considered. Accordingly, it is believed that the present Amendment places this application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, the specification has been amended to include section headings and an abstract as requested by the Examiner. Claims 21 and 22 have been amended to recite that a metal salt is added to a concentrate of the fermented cells and that the pH of the cell concentrate after the addition of the metal salt is less than or equal to 7 in accordance with the teachings in the examples in the present specification. Claims 21 and 22 have also been amended to recite that the production does not include conversion of formed trifulside growth hormone or peptide, respectively, into native peptide form, in accordance with the teachings in the specification, for example, at page 2, lines 23-27. Claim 5 is amended to correspond with claim 21 as amended and claim 23 is added, support for which may be found in the specification, for example, at page 3, lines 8-9. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claims 21 and 22, and claims 3, 5-7, 11-14, 16 and 17 dependent thereon, were rejected under 35 U.S.C. §112, first paragraph. First, the Examiner asserted that there is no antecedent basis for the proviso reciting the exclusion of a peptide refolding step, and, specifically, that the specification disclosure that "there is no conversion of formed trisulfide of growth hormone into the native form" does not support the exclusion of a refolding step. Second, the Examiner asserted that the specification provides no basis for measurement of the pH of the cells but rather that a cell concentrate pH is measured.

These rejections are traversed and reconsideration is respectfully requested. Particularly, present claims 21 and 22 do not exclude a peptide refolding step but rather recite that there is no conversion of formed trisulfide growth hormone or peptide, respectively, into native form, in accordance with the teachings of the specification at page 2. Further, claims 21 and 22 recite a pH of the cell concentration, in accordance with the teachings in the examples. Thus, the present specification provides a written description requirement, whereby claims 21 and 22, and claims 3, 5-7, 11-14, 16 and 17 dependent thereon, comply with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, the rejection has been overcome. Reconsideration is respectfully requested.

The Official Action contains a "claim interpretation" section at pages 5-6. Without commenting on the Examiner's asserted claim interpretation, Applicants merely note that claims should always be given their broadest interpretation consistent with the specification, MPEP §2111.

Claims 6, 7, 11, 12, 14, 16, 17, 21 and 22 were rejected under 35 U.S.C. §102(b) as anticipated by the Aviv et al U.S. Patent No. 5,256,546. The Examiner asserted that Aviv et al teach the production of recombinant human growth hormone in a medium containing K_2PO_4 and NaCl as well as several other metal salts at a pH of 7 +/- 0.2.

However, Applicants submit that the methods defined by claims 21 and 22, and claims 6, 7, 11, 12, 14, 16 and 17 dependent thereon, are not anticipated by and are patentably distinguishable from Aviv et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, independent claim 21 is directed to a method for the production of recombinant growth hormone, comprising fermenting cells to produce recombinant growth hormone. Independent claim 22 is directed to a method for the production of recombinant peptides, comprising fermenting cells to produce recombinant peptides. Claims 21 and 22 specify that a metal salt is added to a concentrate of the fermented cells after the fermentation step, prior to growth hormone isolation (claim 21) or peptide isolation (claim 22). Additionally, the pH of the cell concentrate after the addition of the metal salt is less than or equal to 7. Both claims 21 and 22 further recite the result of reducing the amount of trisulfides formed in a production of the growth hormone (claim 21) or recombinant peptide (claim 22), and the proviso that the production does not include conversion of formed trisulfide growth hormone (claim 21) or peptide (claim 22) into native peptide form after the addition of the metal salt.

On the other hand, Aviv et al disclose in Example 4 at column 16 relied upon by the Examiner an initial bGH production medium containing 2.5 g/l of monohydrogen potassium orthophosphate (K_2HPO_4) and 10 g/l sodium chloride, with a pH of 7 +/- 0.2 maintained with NH_3. However, Aviv et al do not teach addition of a metal salt after fermentation as required by the present claims. Moreover, as Aviv et al teach that the pH is maintained at 7 +/- 0.2, Aviv et al do not conclusively teach that the pH of the medium after addition of the metal salt is less than or equal to 7 as required by claims 21 and 22. On the other hand, the examples set forth in the present specification clearly show that the improvement in trisulfide reduction

is not significant at a pH of 7.2 as compared with a pH of 7.0 or 6.8. Aviv et al provide no teaching or suggestion regarding this criticality.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999). In view of the failure of Aviv et al to disclose a method as recited in claims 21 and 22, wherein, *inter alia*, a metal salt is added to a concentrate of the fermented cells after the fermentation step, whereafter the cell concentrate pH is less than or equal to 7, Aviv et al do not expressly or inherently describe each and every element as set forth in claims 21 and 22. Thus, Aviv et al do not anticipate these claims, or the claims dependent thereon, under 35 U.S.C. §102. It is therefore submitted that the rejection of claims 6, 7, 11, 12, 14, 16, 17, 21 and 22 under 35 U.S.C. §102 based on Aviv et al has been overcome. Reconsideration is respectfully requested.

Claims 3, 5, 6, 11, 13, 14, 16, 21 and 22 were rejected under 35 U.S.C. §102(b) as being anticipated by the Yokoo et al U.S. Patent No. 4,985,544. The Examiner asserted that Yokoo et al teach a method for the production of growth hormone from fish wherein prior to denaturing and renaturing, an alkali metal or an alkali earth metal is added to a precipitate of growth hormone which has been buffered to a pH of 7.

However, Applicants submit that the methods defined in claims 21 and 22, and claims 3, 5, 6, 11, 13, 14 and 15 dependent thereon, are not anticipated by and are patently distinguishable from Yokoo et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The methods of claims 21 and 22 have been discussed above. On the other hand, Yokoo et al teach a process for isolation and purification wherein in a first step (a), cells of microorganisms in which the proteinaceous inclusion bodies have been produced are disrupted and centrifuged to obtain a precipitate A. Specifically, the cells are suspended in a buffer solution having a neutral pH value and subjected to various known disruption methods. The thus-obtained suspension is centrifuged and in a second step (b), the precipitate is suspended in an aqueous solution having dissolved therein solute selected from an alkali metal or alkaline earth metal salt of an inorganic acid, and sugar (column 3, line 15-column 4, line 14). As step (b) of Yokoo et al is conducted after cell disruption, Yokoo et al do not teach the addition of a metal salt prior to growth hormone isolation or peptide isolation, as required by the present claims 21 and 22. Further, Yokoo et al teach that additional

processing of the precipitate of step (b) is required for refolding of the inclusion bodies, i.e., conversion of formed trifulside growth hormone into native growth hormone (see column 4, line 57-column 6, line 68). Thus, Yokoo et al do not disclose a method for the production of recombinant growth hormone or recombinant peptides which does not include conversion of formed trifulside growth hormone or peptide into native peptide form, as required by claims 21 and 22.

In view of these deficiencies in the teachings of Yokoo et al, this reference does not expressly or inherently describe each and every element as set forth in claims 21 and 22. Thus, Yokoo et al do not anticipate these claims, or the claims dependent thereon, under 35 U.S.C. §102. It is therefore submitted that the rejection of claims 3, 5, 6, 11, 13, 14, 16, 21 and 22 under 35 U.S.C. §102 based on Yokoo et al has been overcome. Reconsideration is respectfully requested.

Claims 3, 6, 11-14, 16, 21 and 22 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Christensen WO 96/02570, which is cited at page 2 of the present application. The Examiner asserted that Christensen teaches a method for the production of recombinant hGH which includes the addition of a sulfite for conversion of a hydrophobic derivative of growth hormone into the native form, and a solvent buffered to a pH of about 7.0. The Examiner asserted that it would have been obvious to so treat the growth hormone and then isolate the resulting native growth hormone.

However, Applicants submit that the methods defined by claims 21 and 22, and claims 3, 6, 11-14 and 16 dependent thereon, are nonobvious over and patentably distinguishable from Christensen. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The methods of claims 21 and 22 are discussed in detail above. On the other hand, as set forth in the present specification, Christensen discloses a method for converting a hydrophobic derivative of growth hormone into the native form by chemical treatment with a sulfite compound. Christensen discloses that the hydrophobic derivative contains trifulside (page 3, lines 1-5; page 5, lines 26-31; page 6, lines 14-16; page 9, lines 23-26; and page 10, lines 1-6). Thus, Christensen's method converts the formed trifulside growth hormone into the native form. In contrast, claims 21 and 22 recite methods for the production of recombinant growth hormone or recombinant peptide which do not include conversion of formed trifulside growth hormone or peptide, respectively, into the native form. It is

important to note the distinctions in claims 21 and 22 wherein the present methods reduce the amount of trisulfides formed in the production of the growth hormone or peptide, as compared with a method which forms trisulfide peptide and then requires a step for converting the formed trifulside as taught by Christensen. Thus, the present methods are opposite to those taught by Christensen, and the Examiner has not provided any indication as to how one of ordinary skill in the art would proceed contrary to the teachings of Christensen to arrive at the presently claimed methods. It is error to find obviousness where a reference diverges from and teaches away from the invention at hand, *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). Accordingly, Christensen does not render the methods of claims 21 and 22, or any of the claims dependent thereon, obvious. It is therefore submitted that the rejection of claims 21 and 22, and the claims dependent thereon, under 35 U.S.C. §103 based on Christensen has been overcome. Reconsideration is respectfully requested.

Finally, claims 5-7, 11-14, 16-17 and 21-22 were rejected under 35 U.S.C. §103(a) as unpatentable over the Builder et al U.S. Patent No. 5,663,304. In response to Applicants' previous arguments, the Examiner asserted that the present specification teaches that the production of recombinant proteins in E. coli involves trisulfide bonding, and the Examiner concludes that the presence of a trisulfide bond in a recombinantly produced protein such as growth hormone would be inherent to the recombinant production of the protein.

However, Applicants submit that the methods defined by claims 21 and 22, and claims 5-7, 11-14, 16 and 17 dependent thereon, are nonobvious over and patentably distinguishable from the teachings of Builder et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The methods of claims 21 and 22 have been discussed in detail above. In contrast to the present methods, Builder et al disclose a method of *refolding* misfolded polypeptide, particularly insulin-like growth factor-I, contained in host cells. Builder et al disclose that the "essence" of their invention is utilizing a special buffer containing a minimal concentration of copper or manganese salt to enhance refolding of misfolded polypeptides (column 7, lines 10-12). The special buffer is disclosed as having a pH of 7-12 and comprising about 5-40% (v/v) of an alcoholic or polar aprotic solvent, about 0.2 to 3 M of an alkaline earth, alkali metal or ammonium salt, about 0.1 to 9 M of a chaotropic agent, and about 0.01 to 15 μm of a copper or manganese salt (column 6, lines 42-50).

view that success would have been inherent cannot, in this case, substitute for a showing of reasonable expectation of success; inherency and obviousness are entirely different concepts, *In re Rinehart*, 189 U.S.P.Q. 143, 148 (CCPA 1976). Thus, a reduction in the amount of trisulfides formed in the production of growth hormone or recombinant peptide is not inherent in the specific teachings of Builder et al, and Builder et al provide no teaching or suggestion which would motivate one of ordinary skill in the art to modify the teachings of Builder et al to obtain such a result. Thus, Builder et al do not render the presently claimed methods obvious.

The Examiner also argued that Builder et al teach that potassium chloride is present in the fermentation medium. Importantly, the fermentation medium of Builder et al has a pH of 7.1 to 7.5. Thus, the potassium chloride does not provide a cell concentrate having a pH of less than or equal to 7 after addition of a metal salt. Further, as noted above, Builder et al provide no teaching or suggestion of the addition of a metal salt after fermentation as required by the present claims.

Finally, the Examiner asserts that the additional method steps of Builder et al, including the refolding steps, do not distinguish Builder et al from the claimed methods. However, if Builder et al's refolding step is not considered, then Builder et al provide no suggestion for reducing the amount of trisulfides formed in the production of growth hormone or recombinant peptide, as required by claims 21 and 22. The only method which Builder et al disclose or suggest as suitable for reducing trisulfide in the case of growth hormone is by refolding, i.e., conversion of formed peptide.

To establish prima facie obviousness of the claimed invention, all of the claim limitations must be taught or suggested by the prior art, *In re Royka*, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Furthermore, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (C.C.P.A. 1979). Not only do Applicants find no teaching, suggestion or reference by Builder et al of the method steps recited in claims 21 and 22, Applicants find no teaching, suggestion or reference in Builder et al for modifying the disclosures therein to arrive at the claimed methods. In view of the failure of Builder et al to teach, suggest or recognize the methods as defined by claims 21 and 22, Builder et al do not provide an enabling disclosure of the present methods and therefore do not support a rejection of claims 5-7, 11-14, 15, 17, 21 and 22 under 35 U.S.C. §103. It is

therefore submitted that the rejection of these claims under 35 U.S.C. §103 based on Builder et al has been overcome. Reconsideration is respectfully requested.

It is believed the above represents a complete response to the Official Action and places the present application in condition for allowance. Reconsideration and an allowance are requested.

Respectfully submitted,

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